Trichloroethylene Health Risks—State of the Science

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This monograph comprises 16 articles on the state of the science regarding health risks of trichloroethylene (TCE) that were sponsored by the U.S. Environmental Protection Agency (U.S. EPA), the U.S. Air Force, the U.S. Department of Energy, the National Institute of Environmental Health Sciences, and the Halogenated Solvents Industry Alliance in support of the U.S. EPA trichloroethylene risk assessment. TCE, a chlorinated solvent, was widely used for metal degreasing and is now a common contaminant at Superfund sites and many Department of Defense facilities. TCE has been identified in at least 852 of the 1416 sites proposed for inclusion on the U.S. EPA National Priorities List. Besides being used for degreasing, TCE has been used as an extractant and as a chemical intermediate. Data on environmental releases of TCE are limited. In 1994, 42 million pounds of TCE were released into the environment, as reported to the U.S. EPA Toxic Release Inventory. Most of the TCE used in the United States is released into the atmosphere from vapor degreasing operations. TCE can enter surface waters via direct discharges or groundwater through leaching from disposal operations and Superfund sites; the maximum contaminant level for TCE in drinking water is 5 pbb.

These articles comprise the state of the science on issues related to TCE risk assessment. As part of the publication process, these articles have undergone peer review by the *Environmental Health Perspectives'* editorial board. Staff of the National Center for Environmental Assessment at the U.S. EPA will use these articles to write the health risk assessment for TCE, which will include an integrated summary and risk characterization. The updated risk assessment will be peer reviewed by a panel of experts convened by the U.S. EPA. Comments from the public at large will be a part of this review. The U.S. EPA staff will then address these comments with the goal of making the assessment available in the Integrated Risk Information System (IRIS) (*1*), the U.S. EPA database that contains chemical-specific risk assessment information.

The updated TCE assessment diverges in several respects from the U.S. EPA assessments published more than 12 years ago. First and most important, this assessment emphasizes mode-of-action and pharmacokinetic data to understand and characterize potential noncancer and cancer health risks. To facilitate this, we called on several prominent scientists from both the public and private sectors, many of whom are actively involved in current research on TCE, to author papers that discuss the state of the science on specific issues important to risk assessment for TCE. Second, the dose–response assessment examines newer approaches for evaluating cancer and noncancer effects, including physiologically based pharmacokinetic and biologically based dose–response modeling. This includes approaches discussed in the U.S. EPA revised cancer guidelines, which are changing the ways in which both cancer and noncancer assessments are performed.

The articles are organized according to three of the four elements of the risk assessment paradigm described by the National Academy of Sciences: hazard identification, dose response, and exposure (*2*). The purpose of hazard identification originally was to identify the adverse health effects that might be caused by exposure to an agent. "Hazard identification" has now expanded into "hazard assessment," which seeks to evaluate the relevance of the experimental information to human environmental exposure, characterize the conditions leading to these hazards being expressed in humans, and identify susceptible populations. The TCE assessment emphasizes development of a mechanistic understanding of both cancer and noncancer health hazards. Moreover, such data may be used to inform the dose–response assessment. For example, effects identified in the mechanistic pathway directly related to tumor induction may be judged surrogates for tumors in the dose–response analysis. The first six articles in this volume address hazard issues.

Wartenberg and others (*3*) have reviewed the epidemiologic data. The best evidence for evaluating potential human carcinogenicity is derived from epidemiologic studies, and the epidemiologic evidence on TCE exposure has grown over the past 12 years.

Lash and others (*4*) describe the pathways for TCE metabolism and their cross-species relevance. This article also presents rate constants for several of the oxidative metabolites based on *in vitro* assays, some of which are incorporated into the pharmacokinetic model of Fisher (*5*). Lash et al. (*4*) additionally identify a difference between sexes in metabolite rates, at least for the glutathione-*S*-transferase pathway, which raises questions about susceptibility and sensitive populations, areas of increasing importance in risk assessment.

Pastino and others (*6*) more thoroughly discuss the issues of susceptibility and potentially sensitive populations, in addition to explicitly examining the effects of TCE exposure to children. In a 1994 report *Science and Judgment in Risk Assessment*, the National Academy of Sciences (*7*) emphasized the need to identify, characterize, and include susceptible populations in risk assessment studies. Risks to children received increasing attention after the 1993 National Research Council report on *Pesticides in the Diets of Infants and Children* (*8*). The article by Pastino et al. (*6*) starts this discussion.

TCE has produced an elevated incidence of tumors in rodents in bioassays by both the oral and inhalation routes of exposure. Articles by Moore and Harrington-Brock (*9*), Bull (*10*), Lash et al. (*11*), and Green (*12*) discuss mode-of-action hypotheses for organ-specific tumors. Mode-of-action data have the potential to refine science policy defaults on cross-species scaling and dose–response approaches. Although TCE is a well-studied chemical, the data currently available are considered "mode of action" rather than "mechanism of action" where a detailed understanding of critical events has been identified.

This article is part of the monograph on Trichloroethylene Toxicity.

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The views in this and the following articles are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Received 20 October 1999; accepted 27 October 1999.

Moore and Harrington-Brock (*9*) do not adopt a traditional review of the mutagenicity data on TCE and its metabolites but instead raise several issues regarding the interpretation of mutagenicity and genetic toxicity tests in shedding light on whether these processes are key events in tumor initiation. As discussed in the U.S. EPA proposed cancer guidelines, a salient question is whether TCE or its metabolites interacts directly with and mutates DNA to bring about changes in gene expression or whether DNA mutation is achieved through some other process. The Moore and Harrington-Brock article examines this question.

Bull (*10*), Lash et al. (*11*), and Green (*12*) present the experimental support for several modes of action for tumor development in rodents. These articles discuss a number of hypotheses including the influence on tumor development from mutagenesis, cytotoxicity, cell proliferation, α_{2u}-globin, peroxisome proliferation, oxidative stress, receptor binding, and perturbation of cell-signaling pathways.

Quantitative dose–response issues important to the statistical modeling of both noncarcinogenic and carcinogenic effects are discussed in articles by Fisher (*5*), Bois (*13*), Clewell et al. (*14*), Bois (*15*), Boyes et al. (*16*), Barton and Clewell (*17*), Chen (*18*), and Rhomberg (*19*). Because pharmacokinetic data are available for the TCE assessment, dose metrics other than applied dose may be evaluated in benchmark and other dose–response analyses.

Fisher's article (*5*) describes modeling liver concentration of TCE and its oxidative metabolites, while Clewell et al. (*14*) model plasma concentrations of the oxidative metabolites and flux through the kidney for metabolites of the glutathione-*S*-transferase pathway. Both models are scaled from mice or rats to humans and provide estimates of human equivalent doses simulating inhalation and oral exposure routes.

Parameters from these models have been further subjected to an uncertainty analysis in the articles by Bois (*13,15*). The application of Baysian statistical methods is increasingly used for updating estimates of pharmacokinetic model parameters. Moreover, these analyses can provide an additional set of dosimetric estimates that in some instances are very different from those obtained with the original model. These findings make the risk assessor's job more complex.

Boyes and others (*16*) test whether Haber's Law or a dose metric that integrates time and concentration best describes neurologic effects with high-level TCE exposure.

Barton and Clewell (*17*) examine both experimental and pharmacokinetically derived dose metrics in their analysis of neurologic and systemic organ toxicity seen in the rodent studies. The article further applies benchmark dose methodology to the quantitative analysis of these effects.

The U.S. EPA proposed cancer guidelines recommend that dose–response modeling be carried out in two parts: analysis of the curve shape within the range of the data and extrapolation below the observable data. Application of a biologically based model is preferred for evaluating the dose–response relationship for carcinogenic effects.

Such an approach is described in the article by Chen (*18*), which explores the relationship between TCE and two of its oxidative metabolites, dichloroacetic acid and trichloroacetic acid, under the hypothesis that these chemicals induce liver tumors in mice through promotion of preexisting initiated cells. Unfortunately, the data necessary for supporting a biologically based model are not robust and default dose–response approaches also need to be employed.

Rhomberg (*19*) presents a comprehensive analysis of the liver, lung, and kidney tumor data and pharmacokinetic model-derived dose metrics using default dose–response approaches. Not only does the analysis provide a choice of dose metrics from the two pharmacokinetic models and their uncertainty analyses, which yields four estimates for a single dose metric, it also examines the influence of several metabolites of the cytochrome P450 and glutathione-*S*-transferase pathways. This leads to an examination of the TCE–liver tumor relationship, for example, from multiple perspectives. Finally, Rhomberg attempts to reconcile influences of route of administration on tumor incidence in the inhalation and gavage bioassays by examining systemic and organ-specific dose metrics.

The last article in this series, by Wu and others (*20*), identifies sources, pathways, and routes of exposure as well as enumerates exposed populations. In addition to an examination of TCE, this study examines exposure to the principal metabolites of TCE as well as to other parent compounds that have these as metabolites. It is important to assess background exposure to these compounds as well as how TCE exposure adds to this background.

These articles represent the state of the science for TCE. The challenge ahead for the staff of the National Center for Environmental Assessment is to synthesize the information from these studies to develop the risk characterization for TCE.

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